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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,688	03/22/2001	Katherine A. High	018743-0278737	5212

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/816,688	HIGH ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above claim(s) *5,33,36-40 and 42-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-32,34,35,41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

Claims 1-63 are pending.

Election/Restrictions

Applicant's election of Group I and species SEQ ID NO: 1 and AAV in the reply filed on 4/5/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 5, 33, 36-40, 42-63 and the polypeptide in claim 34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and SEQ ID NO: 2 in claim 9 and adenovirus, parvovirus, papilloma virus, reovirus, rotavirus and herpes virus in claim 31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/7/06.

Upon further consideration SEQ ID NO: 3 in claim 9 and retrovirus in claim 31 is rejoined with the elected species and examined.

Claim Objections

Claim 9 is objected to because of the following informalities: ArgLysArg is missing a SEQ ID NO and has a SEQ ID NO in the CRF. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 7, 8, 10, 13-32, 34, 35 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-4, 6-8, 10, 13-32, 34, 35 and 41, as best understood, are readable on a genus of polynucleotides encoding a modified blood clotting factor, wherein the modification comprises a proteolytic cleavage site or a functional variant thereof, wherein the genus of polynucleotides is not claimed in a specific biochemical or molecule structure that could be envisioned by one skilled in the art at the time the invention was made.

The instant specification contemplates a genus of polynucleotides encoding a modified blood clotting factor, wherein the modification comprises a proteolytic cleavage site not normally present in the factor. The applicant and the prior art teach several proteolytic cleavage site are known in the prior art, including SEQ ID NO: 1, 2, 3, PACE/furin sites, and from a retrovirus Env and Gag polypeptides. The applicant states that, "stretches of basic amino acid residues are known to be cleaved by intracellular proteases" (page 15). Applicant further assert that, " Additional protein cleavage/recognition sites can be identified by sequencing the site of cleavage on a cleaved/secreted protein and determining whether recombinantly introducing the

site into a different protein targeted for secretion mediates cleavage of the protein at the site" (page 15). The specification provides an assay for screening for protein cleaved/recognition sites, but the specification does not provide a sufficient number of species of protein to represent the genus of polynucleotides. The claims read on a broad genus of polynucleotides encoding a modified blood clotting protein, wherein the protein has a proteolytic cleavage site not normally present in the factor. The claims are broader than the disclosure of SEQ ID NO: 1, 2, 3, and PACE/furin sites and proteolytic cleavage sites from retrovirus Env and Gag. The applicants disclose that other proteolytic cleavage sites include those present on virus proteins, which often cellular proteases by intracellular proteases (page 15). There are a number of species and there is variation among species. There is no structure-function correlation between the species disclosed in the specification to the claimed genus. Other than the assertion by applicant that the proteolytic cleavage sites include proteins that utilize cellular processing, the instant specification does not disclose a sufficient number of proteolytic cleavage sites to sufficiently represent the genus of polynucleotides. The instant specification and the prior art do not disclose a number of species of known proteolytic cleavage sites in the art to sufficiently describe the genus of polynucleotides encoding a modified blood clotting protein as set forth in instant claim 1 that must exhibit the disclosed biological function as contemplated by the instant specification. It is not apparent that on the basis of the applicant's disclosure an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the claimed invention and reference to potential methods and/or classes of molecules that are essential for the genus of polynucleotides that must exhibit the disclosed biological functions as contemplated by the specification.

Applicant contemplations that any proteolytic cleavage site recognized by an intracellular protease so that the secreted protein has been cleaved or virus proteins that often utilize cellular proteases for processing are not sufficient to support the present claimed invention directed to a genus of polynucleotides encoding a modified blood clotting protein set forth in the instant claims. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of polynucleotides that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of polynucleotides that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The limitation "wherein the factor is cleaved at the cleavage site when express in an animal cell" in claim 1 does not have patentable under a prior art rejection. See MPEP 2111.

The limitation "wherein the animal cell is mammalian" in claim 15 and "wherein the mammalian cell is human" in claim 16 does not have patentable under a prior art rejection. See MPEP 2111.

The limitation "instructions for expressing the modified blood clotting factor in vitro, ex vivo, or in vivo" in claim 35 does not have patentable under a prior art rejection. See MPEP 2111.

Claims 1, 2, 3, 4, 6-12, 15, 16, 21, 22, 23, 24, 25, 26, 27, 29, 30, 31, 32, 34, 35, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Himmelspach et al. (WO 98/38317).

NOTE: US 6,573,071 is the English equivalent of the WO document because '071 is dependent on the application that the WO document is based on.

Himmelspach teaches a nucleic acid encoding factor X analogue with a modified cleavage site (abstract, columns 4 and 9, and Figures 2 and 7-8). Himmelspach teaches using PACE/furin (column 5). Factor X is from a human (column 9). Factor X can be in a composition comprising a pharmaceutical carrier (columns 11-13). The nucleic acid encoding

Factor can be inserted into an expression system (vector, retrovirus) comprising a suitable promoter, beta-actin (columns 13-14). The cleavage can comprise SEQ ID NO: 3 of the instant application (column 16). Furthermore, the skilled artisan understands that a retroviral envelope protein cleavage site comprises SEQ ID NO: 3 of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 24, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Himmelspach et al. (WO 98/38317) taken with Amalfitano et al. (US 6328958).

NOTE: US 6,573,071 is the English equivalent of the WO document because '071 is dependent on the application that the WO document is based on. The description below uses the specification of '071.

Himmelspach teaches a nucleic acid encoding factor X analogue with a modified cleavage site (abstract, columns 4 and 9, and Figures 2 and 7-8). The nucleic acid encoding Factor can be inserted into an expression system comprising a suitable promoter (columns 13-14). However, Himmelspach does not specifically teach using an expression control element comprising elongation 1alpha promoter.

However, at the time the invention was made, Amalfitano teaches a heterologous nucleotide sequence (e.g., clotting factor) operatively associated with a cytomegalovirus (CMV) major immediate-early promoter, an albumin promoter, an Elongation Factor 1-.alpha. (EF1-.alpha.) promoter, a P.gamma.K promoter, a MFG promoter, or a Rous sarcoma virus promoter. See columns 19-20.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Himmelspach taken with Amalfitano, namely to produce the composition comprising an EF1-alpha promoter. One of ordinary skill in the art would have been motivated to combine the teaching to sufficiently express Factor X in a cell.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1, 3, 4, 13, 14, and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Himmelspach et al. (WO 98/38317) taken with Berkner (US 5288629).

NOTE: US 6,573,071 is the English equivalent of the WO document because '071 is dependent on the application that the WO document is based on. The description below uses the specification of '071.

Himmelspach teaches a nucleic acid encoding factor X analogue with a modified cleavage site (abstract, columns 4 and 9, and Figures 2 and 7-8). The nucleic acid encoding Factor can be inserted into an expression system comprising a suitable promoter (columns 13-14). However, Himmelspach does not specifically teach using a nucleic acid encoding Factor VII with a modified cleavage site.

However, at the time the invention was made, a nucleic acid encoding Factor VII was well known to one of ordinary skill in the art as exemplified by Berkner (columns 1-3). A cleavage site of Factor VII is between arginine 152 and isoleucine 153 of Factor VII (Figure 1).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Himmelspach taken with Berkner, namely to produce a nucleic acid encoding factor VII analogue with a modified cleavage site. One of ordinary skill in the art would have been motivated to combine the teaching to increase the stability of Factor VII in a cell.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Himmelspach taken with Berkner, namely to produce a nucleic acid encoding factor VII analogue with a modified cleavage site between arginine 152 and isoleucine 153. One of ordinary skill in the art would have been motivated to combine the teaching because a proteolytic cleavage site of Factor VII is between these two amino acids.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Willis (US 5,175,099). Willis teaches producing a retroviral vector comprising a gene encoding a fusion protein having an engineered cleavage site from a retrovirus (column 4). Willis teaches that a retroviral vector secretes proteins in soluble form into culture medium and the secretion occurs via the normal intracellular pathway (column 3). The secreted proteins are not contained in membrane vesicles or particles (column 3). This fusion protein can be used for protein purification (abstract).

Moulard et al. (Biochemistry 1998, 37, 4510-4517). Moulard teaches that a retroviral envelope contains a proteolytic cleavage site consisting of the amino acid sequence (Arg/Lys-Xaa-(Arg/Lys)-Arg).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman
Patent Examiner, Group 1635

BRIAN WHITEMAN
PATENT EXAMINER